Risk Evaluation and Mitigation Strategies (REMS):
Focus on Erythropoietic Stimulating Factors

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At the end of this presentation, the audience should be able to:

- Describe a Risk Evaluation Mitigation Strategy and why they were developed by the FDA
- List the components of a REMS strategy
- Provide examples of medications requiring a REMS
- List the advantages and disadvantages of a REMS and any potential consequences they may have on pharmacotherapy

The Belmont Report - Beneficence

- Requires researchers to minimize the risks of harm and maximize the potential benefits of their work.

http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm
What is FDAAA?

- **Food and Drug Administration Amendments Act of 2007**
- The President signed into law, FDAAA on September 27, 2007 before certain laws were set to expire on September 30, 2007
- FDAAA is the legislation that adds many new provisions to the FD&C Act to provide important resources and strength to the agency’s ability and commitment to safeguard and advance public health


Food and Drug Administration Amendments Act (FDAAA) of 2007

- **New Safety Authorities under FDAAA Title IX**-
  - Require postmarketing studies and clinical trials
  - Require sponsors to make safety related labeling changes
  - Require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS)
- **New authorities effective 180 days after enactment of FDAAA, March 25, 2008**

Risk Management before FDAAA

- Belmont principle: Beneficence
- Most basic risk management tool, was, and still is, the labeling directed to prescribers
  - Labeling contains directions for use, warnings, precautions, contraindications, and underlying data on efficacy and safety
- In some cases, the labeling might include a Medication Guide or Patient Package Insert with information directed to patients

When a drug posed more significant risks, a risk management plan might be agreed upon; plans included a range of risk management tools from education to restricted distribution of the drug

- 16 drugs were approved with restricted risk management programs before FDAAA
  - thalidomide – S.T.E.P.S Program
Risk Management Pre-FDAA: RiskMAPs

- Before FDAAA, a small number of drug and biological products were approved with risk minimization action plans (RiskMAPs).
- RiskMAPs:
  - Designed to meet specific goals and objectives to minimize known risks while preserving its benefits
  - Developed for products that had risks that required risk management strategies beyond the required labeling and safety reporting.

In 2005, FDA issued a Guidance for Industry on Development and Use of Risk Minimization Action Plans* describing how to:
- Develop RiskMAPs,
- Select tools to minimize risks,
- Evaluate and monitor RiskMAPs and monitoring tools and
- Communicate with FDA about RiskMAPs

FDAAA clarified FDA’s authority to require enforceable risk management programs (REMS)
REMS were built on previous experiences with RiskMAPs

REMS

- Definition: A Risk Evaluation and Mitigation Strategy (REMS) is a strategy and plan to manage and assess a known or potential serious risk associated with a drug or biological product.

- FDA can require sponsors to develop and implement REMS for prescription drug and biological products approved under:
  - New Drug Applications (NDAs)
  - Abbreviated NDAs (ANDAs), and
  - Biological license applications (BLAs)

REMS

Section 505-1 states the FDA may require a REMS:

- Before approval: If FDA determines a REMS is necessary to ensure that the benefits of the drug outweigh its risks

- Post approval: If FDA becomes aware of new safety information and determines a REMS is necessary to ensure the benefits of the drug outweigh its risks

Once notified by FDA that a REMS is necessary, the holder must submit a proposed REMS
**REMS**

- ANDAs for which the reference listed drug has a REMS will be approved with the elements of that REMS applicable to ANDAs

- REMS are enforceable
  - Drug may found to be misbranded,
  - FDA can impose civil penalties for violation of the Act

**Deemed REMS**

- Section 909 stated that drugs approved before FDAAA with elements to assure safe use were deemed to have REMS

- In 2008, FDA published a list of drugs that were identified as deemed to have an approved REMS

  - As of October 7, 2011:

<table>
<thead>
<tr>
<th>Tracleer</th>
<th>Isotretinoin</th>
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</thead>
<tbody>
<tr>
<td>Letairis</td>
<td>Mifepristone</td>
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<tr>
<td>Thalomid</td>
<td>Actiq</td>
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<td>Revlimid</td>
<td>Tikosyn</td>
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<td>Lotronex</td>
<td>Tysabri</td>
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Factors determining the need for a REMS

- Size of the population likely to use the drug
- Seriousness of the disease
- Expected benefit of the drug
- Expected duration of treatment
- Seriousness of known or potential adverse events
- Whether the drug is a new molecular entity

REMS Elements

- Only required element is a timetable for submission of assessments of the REMS
- Sponsors submit evaluation of the effectiveness of the REMs:
  - Required a minimum of 18 months, 3 years and 7 years after approval (more frequently with REMs with ETASU)
  - REMS approval letter will include specifics for assessment plan
  - Sponsor develops assessment methods, but FDA can require additional assessments
- FDA requires each REMS to have a goal against which it can be assessed
Elements of a REMS

- Medication Guides (when applicable) and Patient Package Insert (PPI) (if insert, may help mitigate serious risk of the drug)
- Communication plan if FDA determines plan may support implementation of an element of the REMS
- Elements to assure safe use (ETASU)
- Implementation system, if REMS includes certain ESASUs

Medication Guides

- FDA requires that Medication Guides be dispensed with certain prescribed drugs and biological products when:
  - Certain information is necessary to prevent serious adverse effects
  - Patient decision-making should be informed by information about a known serious side effect with a product, or
  - Patient adherence to directions for the use of a product are essential to its effectiveness
Medication Guides

- Medication Guides will NOT be a common element in a REMS (Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies)
  - FDA may approve a MG without requiring a REMS when labeling is adequate to address the serious and significant public health concerns
  - REMS may still be included in REMS and are subject to the assessment and modification process required under FDAAA
  - Elimination of MG-only REMS, the number of patients surveys will decrease

Communication Plan

- A Communication Plan for health care providers may be a required element by FDA if it may support implementation of REMS
  - May include
    - Sending letters to health care providers
    - Disseminating information about REMS elements to encourage implementation by health care providers or to explain certain safety protocols, such as laboratory monitoring
    - Disseminating information to health care providers through professional societies about serious health risks of the drug and any protocol to assure safe use
Elements to Assure Safe Use (ETASU)

Examples:
- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry


ETASU: Certification of Healthcare Providers

- A REMS may require healthcare providers who prescribe the drug to have particular training or experience, or to be specially certified
- Certifications may require, for example, that prescribers:
  - Are familiar with educational materials, risks of the drug, and conditions for safe use
  - Can diagnose and treat potential adverse reactions or are familiar with required monitoring
ETASU: Certification of those who Dispense

- A REMS may require pharmacies, practitioners, that dispense the drug to be specially certified or dispense the drug in certain healthcare settings

- Certifications may require, for example, that dispensers:
  - Are familiar with educational materials, risks of the drug, and conditions for safe use
  - Agree to fill a prescription only after receiving prior authorization

ETASU: Certification of those who Dispense (continued)

- Certifications may require, for example, that dispensers:
  - Provide and/or administer the drug only in hospitals or infusion centers
  - Provide evidence of safe-use conditions
    - Laboratory tests
    - Documentation of consent or counseling by patient
    - Patients receive the drug only after specified authorization is obtained (e.g., documented negative pregnancy test)
ETASU Miscellany

Patient Monitoring
- REMS may require each patient using the drug to be subject to certain monitoring
  - Periodic blood tests or other monitoring at specified times
  - Follow-up questionnaire at specified time periods

Registry
- REMS may require enrollment in a registry
  - Patient information to allow follow-up on adverse events and trends

Implementation Systems
- REMS may include an implementation system to ETASU in certification of pharmacies and hospitals, dispense only in certain healthcare settings, and safe use conditions
  - May require reasonable steps to:
    - Monitor and evaluate implementation of such elements by health care providers, pharmacists, and other parties who are responsible for implementing such elements, and
    - Work to improve implementation of such elements by such persons
Isotretinoin
PPP ➔ SMART ➔ I-PLEDGE

- Applications Development and Hosting
- Adverse Event Management
- Data Analysis and Reporting
- Document production and fulfillment
- Patient surveys via web and IVR
- Call Center Management
- Pregnancy Registry
- Education Materials Design & Update
- Assessments
- Performance-Linked Access System requiring pregnancy test results and contraception choices


REMS to date:
(March, 2008-October 2011)

- New REMS approved for about 185 products
  - 124 Medication Guide-only REMS (73 released)
  - 61 REMS including more than a Medication Guide
    - 21 have elements to assure safe medication use and possibly other elements such as a communication plan or Medication Guide
    - 40 had a communication plan as the primary element and most also had a Medication Guide
MMC formulary: REMS drugs requiring > MG, CP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date REMS approved</th>
<th>REMS components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aranesp (darbepoetin alfa)</td>
<td>2/6/10, modified 6/24/11</td>
<td>MG, CP, ETASU, IS</td>
</tr>
<tr>
<td>Avandia (Rosiglazone)</td>
<td>5/18/11</td>
<td>MG, CP, ETASU, IS</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>10/22/10</td>
<td>MG, ETASU, IS</td>
</tr>
<tr>
<td>Mifepristone (mifepristone)</td>
<td>6/8/11</td>
<td>CP, ETASU, IS</td>
</tr>
<tr>
<td>Nplate (romiplostim)</td>
<td>8/22/0, modified 8/14/9, 3/23/10</td>
<td>MG, CP, ETASU, IS</td>
</tr>
<tr>
<td>Oxycontin (oxycodone CR)</td>
<td>4/5/10; modified 6/29/10, 11/15/10</td>
<td>MG, ETASU</td>
</tr>
<tr>
<td>Promacta (eltrombopag)</td>
<td>11/20/8; modified 3/5/10, 1/25/11</td>
<td>MG, ETASU, IS</td>
</tr>
<tr>
<td>Revlimid (lenalidomide)</td>
<td>8/3/10</td>
<td>MG, ETASU, IS</td>
</tr>
<tr>
<td>Sabril (vigabatrin)</td>
<td>8/21/9, modified 1/18/11</td>
<td>MG, CP, ETASU, IS</td>
</tr>
<tr>
<td>Suboxone (buprenorphine &amp; naloxone)</td>
<td>8/30/10</td>
<td>MG, ETASU, IS</td>
</tr>
<tr>
<td>Thalidomide (thalidomide)</td>
<td>8/3/10</td>
<td>MG, ETASU, IS</td>
</tr>
<tr>
<td>Tikosyn (dofetilide)</td>
<td>7/11/11</td>
<td>MG, ETASU, IS</td>
</tr>
<tr>
<td>Tracleer (bosentan)</td>
<td>8/7/9; modified 2/19/10</td>
<td>MG, ETASU, IS</td>
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MG – Medication Guide, CP – Communication Plan; ETASU – Elements to Assure Safe Use; IS – Implementation System

REMS: 4 Years of Experience

- Public meetings to obtain stakeholders views on the program
  - FDA: July 2010
    - > 60 individual presentations to obtains views on the program
    - Issues and challenges identified
    - Survey of members

http://www.fda.gov/Drugs/NewEvents/ucm210201.htm
CSDD – Survey Results

- Three-quarters of respondents said the REMS program needs a major overhaul.
- 68% said that REMS are a poor substitute for other improvements needed system-wide in drug education, communication, monitoring of use, patient access and delivery of care.
- 86% felt that under current guidelines, risk and benefit information was not well balanced in REMS communications.
- Only 22% of respondents thought the REMS program has been an improvement over the existing risk management system.


REMS: Pros, Cons

Pro
- REMS or alternative are necessary to preserve access to drugs whose risks would otherwise exceed benefits

Con
- Multiplicity of unique REMS places burdens on the healthcare system
  - Particularly, REMS with elements to assure safe use
- Patients may not be well informed of Risks and benefits
REMS: Suggestions

Suggestions
- Standardized REMS programs would reduce burden on the healthcare system
- Use informatics to implement, manage REMS more efficiently and effectively
- Consult with prescribers, pharmacists, patient groups
  - How to design REMS so that they preserve access while effectively addressing risk

REMS: Darbepoetin alfa (Aranesp) - APPRISE*

- REMS elements
  - Medication Guides (in accordance with 21 CFR Part 208)
  - Communication Plan
    - Healthcare Professional Communication
    - ESA Apprise Oncology Program Website
  - ETASU
    - Be specially certified to prescribe and dispense darbepoetin alfa (Apprise)
  - Implementation System
    - Amgen will monitor compliance with documentation of risk/benefit discussion and completion of Patient and Health Care acknowledgment form
    - Timetable of submission of Assessments
      - 8 months, 1 year, 18 months, 24 months, annually

*Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs
CPOE Medication Order pad

Physician templates ESA order
Physician attestation

Order awaiting pharmacy processing
Pharmacist places order from template with physician name

MMC Aranesp REMS to date

- Implemented January 16, 2011
- Average # doses/month – 18
The Belmont Report- Autonomy (Respect)

Principles:
- Autonomy (Respect)
  - Requires researchers to treat individuals as autonomous human beings
- Rules derived from the principle of respect for persons include:
  - The requirement to obtain and document informed consent.
  - The requirement to respect the privacy interests of research subjects.
  - The requirement to consider additional protections when conducting research on individuals with limited autonomy


To sign or not to sign…That is the question

- Decision to sign or not sign a consent form is based more on a "gut feeling", trust from provider

- 80% of signed consents aren’t read at all
  - Consent process
  - Consent readability
  - Consent format
Consenting process: What did you say?

- Continuous attention span, or the amount of time a human can focus on an object without any lapse at all, is very brief and may be as short as 8 seconds.

- The average attention span of an adult is 20 minutes.

Consent Readability: Huh?


- Hypothesis: that text provided by IRBs in informed consent forms falls short of the IRBs own readability standards.

- A total of 114 Web sites of U.S. medical schools were surveyed for IRB readability standards and informed-consent-form templates. Actual readability was measured with the Flesch–Kincaid scale, which assigns a score on the basis of the minimal grade level required to read and understand English text (range, 0 to 12).
Readability Standards for Informed Consent Forms as Compared with Actual Readability

- Among the 61 schools with specific grade-level standards, only 8% met their own standards
- The mean score for readability exceeded the stated standard by 2.8 grade levels (Flesch–Kincaid scale)
- In a sub-sample from 24 medical schools, the modal score for readability (Fry scale) was 13 (range, 6 to 16)

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Consent Readability

- 1 in 2 Americans cannot read above a 5th grade reading level (Kirsch, 2003)
  - 55% are at or below basic skills at quantitative literacy
- Most patient education materials are written beyond a recipient’s ability to understand (IOM 2004)
Consent Readability

Flesch – Kincaid score:
8.2

Consent format

Truly Informed?

MEDICATION GUIDE
Aranesp® (Air-uh-nesp) (darbepoetin alfa)

Read this Medication Guide:
• before you start Aranesp,
• if you are told by your healthcare provider that there is new information about Aranesp,
• if you are told by your healthcare provider that you may inject Aranesp at home, read this Medication Guide each time you receive a new supply of medicine.

This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Talk with your healthcare provider regularly about the use of Aranesp and ask if there is new information about Aranesp.

What is the most important information I should know about Aranesp?

Using Aranesp can lead to death or other serious side effects.

For patients with cancer:

Your healthcare provider has received special training through the ESA APPRISE Program in order to prescribe Aranesp. Before you can begin to receive Aranesp, you must sign the patient healthcare provider acknowledgment form. When you sign this form, you are stating that your healthcare provider talked with you about the risks of taking Aranesp.

These risks include that your tumor may grow faster and you may die sooner if you choose to take Aranesp.

You should talk with your healthcare provider about:
• Why Aranesp treatment is being prescribed for you.
• What are the changes you will get red blood cell transfusions if you do not take Aranesp.
• What are the changes you will get red blood cell transfusions even if you take Aranesp.
• How taking Aranesp may affect the results of your cancer treatment.

After you have finished your chemotherapy course, Aranesp treatment should be stopped.

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Risk of transfusions

- Acute hemolytic reactions (e.g., fever, chills, chest pain, back pain, hemorrhage, tachycardia, SOB)
- Febrile non-hemolytic reactions
- Allergic reactions
- Transfusion-associated acute lung injury
- Infection (e.g., HIV, hepatitis, Chagas disease, cytomegalovirus)
- Post-transfusion purpura
- Volume overload
- Metabolic complications
- Medical error – wrong blood type infused
- Increased cost
- Increased time spent in medical facility

Decisions, Decisions!

PASSIVE

- Forgetfulness
- Lack of understanding
- Health Literacy
- Miscommunication

ACTIVE

- Experience
- Fear
- Stigma
- Denial
- Health Belief System
REMS element: Sponsors submit evaluation of the effectiveness of the REMs:

- Aranesp REMS goal(s)
  - To support informed decisions between patients and their healthcare providers who are considering treatment with Aranesp by educating them on the risks of Aranesp
  - For treatment of patients with cancer, the goal of the REMS, as implemented through the ESA Apprise, is to mitigate the risk of overall shortened survival and/or increase risk of tumor progression or recurrence
    - Research or QI?

Conclusions

- The REMs program:
  - Provides patient access to effective medication that would not otherwise be available due to potentially serious adverse events
  - Attempts to reduce the risk of serious AEs via several mechanisms including education, monitoring and restricted access

- Limitations of REMS include:
  - Lack of standardization makes it difficult to administer or manage
  - Unbalanced Risk/Benefit information and comprehension
  - Unclear if program can actually mitigate risk
Components of a REMS include

1. Drug Package Insert distributed to patients to help mitigate serious risk of the drug
2. Emails and public service announcements to the public detailing the risks of the drug
3. Healthcare providers who prescribe the drug have particular training or experience or special certifications
4. Stocking the drug in all community pharmacies to prevent delays in dispensing and administration of lifesaving medications